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10/709,691	05/24/2004	Itzhak Bentwich	050992.0400.01USCP	3690

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/709,691	BENTWICH ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008 and 25 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25,31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/24/2008 and supplemental submission on 11/25/2008 have been entered.

Status of Application/Amendment/Claims

Applicant's response filed 11/24/2008 and 11/25/2008 have been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/23/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 23, 25, 31, and 33 are pending and under consideration.

Specification

The specification is objected to because it refers to Tables 1-11 at paragraph 33 and elsewhere but the paper specification as filed does not contain any Tables labeled 1-11. The

specification indicates that Tables 1-13 were supplied on CDs and are incorporated by reference (paragraph 27). However, such incorporation by reference appears to be improper since it does not state with particularity, as by section, line, or page number, what material therein is being relied on and where that material may be found.

MPEP 608.01(p) indicates that in any application that is to issue as a U.S. patent, essential material may only be incorporated by reference to a U.S. patent or patent application publication. The Tables in question, and the essential information therein, are not a U.S. patent or a patent application publication. Note also that MPEP 608.01(p) indicates that when incorporating material by reference "[p]articular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found." In incorporating the tables by reference, Applicant makes no specific references to which portions of any of tables 1-13 in particular are relied on for support of the claimed subject matter.

The U.S. Court of Appeals, Federal Circuit, in *Zenon Environmental Inc. v. United States Filter Corp.*, 85 USPQ2d 1118 (Fed. Cir. 2007) stated that "To incorporate material by reference, the host document must identify with detailed particularity what material it incorporates and clearly indicate where that material is found in the various documents." (page 1124). With regard to the incorporation of tables 1-13 by reference, Applicant has not fulfilled these essential requirements.

The Examiner further notes the descriptive matter of an application should be limited to or at least be pertinent to that which is claimed. Tables 1-13 would appear to disclose hundreds of thousands of unrelated sequences and several megabytes of information unrelated to those now claimed. Thus, the application contains a lengthy disclosure entirely outside the bounds of

the claims. Applicant is required to restrict the descriptive matter so as to be in harmony with the claims (MPEP § 1302.01) while avoiding new matter changes.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25, 31, and 33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a credible asserted utility or a well established utility.

The claims are drawn to isolated polyribonucleotide sequences, 22 and 91 nucleotides in length, referred to therein as SEQ ID NO: 348 and 423864, respectively. The application further claims the complements of said sequences and DNAs of the same length encoding said sequences as well as expression vectors thereof. The sequences were originally identified bioinformatically, using a computational method designed to screen raw genomic data for putative microRNA (miRNA) sequences. Accordingly, the claimed sequences represent bioinformatically predicted mature and pre-processed miRNAs. The specification asserts that all such sequences, including those specifically claimed, may be used to regulate the expression of certain specific genes, identified in various tables incorporated by reference. The specification contains no experimental data directly relevant to the instantly claimed sequences, or for that

matter any other bioinformatically predicted sequence, to represent or support the asserted utility. Accordingly, the credibility of the asserted utility rests entirely on the accuracy of the bioinformatic prediction method, and, when available, well-established utilities of mature 22-nucleotide and pre-processed (~80-100 nt) miRNA sequences. There is no either in the instant application or in the pre- or post-filing art clearly articulating the sensitivity or false positive rate of the instant algorithm, nor any data to substantiate its use as a reliable indicator of miRNA function and target specificity.

Over the course of prosecution (Remarks filed 6/29/07, 3/17/08, and 11/24/08), Applicant has asserted, with support from the specification, the mature miRNA sequence corresponding to SEQ ID NO:348 specifically targets and inhibits mRNAs corresponding to human SERPINH1, MGAT5, and, most recently, uracil DNA glycosylase. Apparently, the instantly claimed miRNA sequences are capable of regulating multiple different genes. A review of the miRNA Registry and TargetScan shows the instant miRNA, referred to in the database as has-miR-497, contains the necessary 8-base seed sequence to suggest it may potentially target many dozens of different genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification teaches a bioinformatic method for detecting putative miRNA-like precursor sequences in the genome of an organism. Further bioinformatics processing is then used to predict the single stranded miRNAs likely produced from such sequences. Finally, the

sequences of the predicted miRNAs are compared to sequences of known genes to identify potential targets and possible biological functions of the miRNAs.

While the specification teaches miRNA prediction, support is not readily found showing that the claimed miRNAs are actually produced in any cell or organism, or even if produced artificially, would lead to any biological effect of any immediate, real world value. No biologically relevant data, nor any intrinsic or extrinsic evidence is found in the instant application confirming any of the asserted utilities.

While the claimed nucleic acids would have a specific and substantial utility if said nucleic acids in fact inhibit a known gene having a known function, there is no direct or indirect evidence that the claimed nucleic acids, in fact, inhibit the expression or translation of any gene, much less the genes said to be specifically targeted by the claimed nucleic acids.

Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets. Neither the accuracy nor false-positive rates of the algorithm used for prediction have been made of record, and there is absolutely no evidence that the bioinformatically predicted sequences, which typically possess much less than 100% complementarity with the predicted target, have the utility asserted by the computer prediction method. Even if the level of complementarity is typical of mammalian miRNAs, the assertion that a bioinformatically predicted miRNA will inhibit a specific gene would be deemed credible only if there were sufficient evidence to indicate one of skill would believe the predicted utility was more than likely correct even without any corroborating experimental evidence. Currently, the Examiner finds no such evidence in the prior art or application.

Post-filing art indicates that while prediction software and bioinformatics methods significantly narrow the field of possible miRNA sequences, they do not substitute for or render unnecessary the need for biological validation.

Bentwich (2005) *FEBS Lett.* 5904-5910 teaches that biological validation is necessary to raise the specificity and sensitivity of microRNA prediction algorithms, implying that predictions based on such algorithms need validation and that prediction does not guarantee that such a sequence exists or has the function assigned to it by the software.

Watanabe et al. (2007) "Computational Prediction of miRNA Targets" *Methods Enzymology* 427:65-86 teach at page 82 that experimental validation of miRNA target interactions is crucial to detecting novel miRNA targets, as computational methods are not perfect, and there is a risk of false-positive prediction. At page 81 it is said validation of computational prediction algorithms and predicted miRNA targets is crucial for understanding the biological significance of prediction results.

Martin et al. (2007) *J. Biosci.* 32:1049-1052, reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by

miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.

In general comparative miRNA prediction algorithms used in the art are said to have false positive rates of between 22% and 39%. See Bentwich et al. (2005) *FEBS Lett.* 579:5904-5910, page 5907; and the Declaration filed 3/17/08, Point 4. See also Martin et al. (2007) *J. Biosci.* 32:1049-1052 at page 1049, 4th full paragraph.

Furthermore, the post-filing art suggests that it is difficult to estimate the true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known. See Maziere et al. (2007) *Drug Discovery Today* 12:452-458, page 457. Maziere et al. in their article entitled "Prediction of miRNA Targets," further state that comparison of miRNA prediction efficiencies among different programs is not currently possible because many of the programs are not available for download and use on a common dataset; thus, Maziere et al. cast doubt on the reliability of the statements made in the Declaration, comparing similar programs to that used by the Inventor. Again, no evidence has been presented by Declarant directly comparing the output of the instant algorithm with the other cited programs when presented with a common dataset. Thus, there is no objective evidence to corroborate Declarant's opinion.

Smalheiser et al. (2006) *Methods Mol. Biol.* 342:115-127 in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential importance of mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts

within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential mRNA targets from being effectively silenced by the RNA-induced silencing complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs interact with their targets via "short seeds," complementary regions of 6-8 nucleotides, but, instead, may interact via "long" seeds and perfect matches (page 115-6), and because new miRNAs are constantly being discovered this list of binding determinants may not be complete.

Accordingly, even as recently as 2007, those of skill in the art recognized the importance of biological validation of bioinformatically predicted miRNAs. Clearly, the art teaches that multiple factors are involved in miRNA-target binding and recognition. Thus, in the absence of supporting biological data, there is sufficient reason to believe one of skill at the time of filing would question the objective truth of the statements in the specification that the instantly claimed sequences may be used to regulate a particular gene identified solely on the basis of a bioinformatic algorithm. One of skill would have recognized the need for de novo testing to verify the utility.

Other factors are also important to the consideration for lack of credible utility. In particular, the prior and post-filing art suggests that microRNA target specificity and function depends on the production of a dsRNA (miRNA:miRNA duplex) intermediate comprising the mature microRNA. See Cullen (2004) "Derivation and function of small interfering RNAs and microRNAs" *Viral Res.* 102:3-9, pages 4-6 and Fig. 1; and Bartel et al. (2004) *Cell* 116:281-297, pages 285-288. This intermediate is required for effective incorporation of the miRNA guide strand into the RISC. Currently, there is no evidence the instantly claimed single stranded 22-mer, SEQ ID NO:348, which has at most 7 or 8 contiguous nucleotides complementary to the

proposed target gene, would regulate the target gene on its own if transfected or endogenously expressed as the single stranded 22-mer in the cell. Indeed, given its single stranded nature and low partial complementarity to the target, one of skill would reasonably question its ability to act alone as a sequence-specific RNAi agent or antisense-based translational repressor. Rather, the art clearly teaches that, to enter the RISC pathway and carry out functions associated with microRNAs, the miRNA must be double stranded. Single stranded 22-nucleotide RNAs that have low partial complementarity to a gene target, such as that now claimed, do not have a clear, well established utility as either an antisense oligonucleotide or a reliable probe.

While the 91-nt, partially self-complementary miRNA precursor sequence SEQ ID NO:4233864 may reasonably be a substrate for dicer-catalyzed cleavage, and give rise to a dsRNA intermediate capable of inhibiting the expression of the asserted target gene, there is no evidence of record to show a short dsRNA intermediate comprising SEQ ID NO:348 is a product derived from said cleavage, or any evidence to show that the transfection or endogenous expression of SEQ ID NO:4233864 leads to the sequence specific inhibition of any of the proposed target genes. Given the large number of potential targets identified in the public database, there is reason to believe that many genes would be inhibited, leading to complex array of effects but no specific effect.

Accordingly, currently, there is not data to substantiate the assertion that either the 22-nucleotide miRNA corresponding to SEQ ID NO:348 or precursor miRNA corresponding to SEQ ID NO:4233864 may be used to sequence-specifically inhibit SERPINH1, MGAT5, or uracil DNA glycosylase.

Thus, in view of the totality of the evidence, one of skill would have reason to doubt the objective truth of the asserted utility. While the instant algorithm provides a list of putative miRNAs and corresponding target sites, there is reason to question whether the bioinformatic algorithm used to produce this list correctly identifies an miRNA and its function (i.e., at least one biological function) with minimally acceptable false positive and false negative rates such that one of skill would believe the miRNA would, more likely than not, inhibit the gene predicted by the software. Without experimental validation or any verifiable evidence of the accuracy and error rates of the instant program, and in view of the state of the art at the time of invention, one of skill would reasonably question the certainty of the prediction at the time of filing. The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

***

Claims 23, 25, 31, and 33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments/Declaration under 37 CFR §1.132

Applicant's arguments filed 11/24/2008 and the Declaration under 37 CFR 1.132 by Ayelet Chajut filed 11/25/2008 have been fully considered but are insufficient to overcome the rejection as applied to claims 23, 25, 31, and 33.

The Declaration shows that sequences antisense to SEQ ID NO:348 (has-miR-497) interfere with or block the cleavage UNG mRNA. The effect is similar to that taught by Zamore et al. (2004) *PLoS Biology* 2(4):0465-0475, whereby miRNA-directed mRNA cleavage is effectively blocked by transfection with an oligonucleotide complementary to the mature miRNA. Thus, the declaration shows that oligonucleotides complementary to SEQ ID NO:348 may be used to inhibit hsa-miR-497 activity in a cell. While these data may show a specific, substantial, and credible utility for the 21- antisense oligonucleotide used in the analysis (see Declaration) inasmuch as the oligonucleotide may be used to specifically inhibit has-miR-497 and thereby cleavage of UNG, and while this oligonucleotide may be sufficiently representative of the 22-nt complement of SEQ ID NO:348 as claimed in Claim 23, Part c, the data do not show or reasonably represent the utility of SEQ ID NO:348 itself or SEQ ID NO:4233964 or the DNAs encoding said sequences. The data shown in the Declaration are partially but not fully commensurate with what is now claimed. The data do not address the unpredictability, described in the rejection above, with regard to the activity of the mature single stranded 22-nt miRNA and its purported precursor, SEQ ID NO:4233864. While it is reasonable to presume a double stranded precursor miRNA sequence would be a substrate for the RISC/miRNA pathway, the Examiner is unable to find any credible evidence teaching or suggesting that single stranded, partially complementary mature 22-nt miRNAs are substrates for RISC or useful in any conventional sense on their own as sequence-specific blocking reagents. Accordingly, the Declaration filed 11/24/08, while pertinent to an embodiment in Part c of Claim 23, is insufficient to obviate the rejection as applied the other remaining sequences expressly claimed.

Applicant argues the instantly claimed sequences satisfy the specific and substantial standards of the utility requirement. The Examiner agrees inasmuch as the sequences are said to be capable of inhibiting a specific gene having a known function.

Applicant presents additional remarks addressing the data supplied by declaration. While the Examiner agrees the data adequately show that has-miR-497 (SEQ ID NO:348) is expressed and most likely inhibits UNG, the data do not show that the isolated sequence on its own has any utility, since there is reason to believe the single stranded sequence lacks the requisite properties to be properly incorporated into the miRNA/RISC pathway, and because the sequence is much less than 100% complementary to the alleged target gene to be expected to act as a conventional antisense agent.

While one of skill might reasonably believe the double stranded precursor sequence, SEQ ID NO:4233864, would enter the RNAi pathway and inhibit gene expression, there is reason to question the specific utility because there is no data to substantiate the function, which one of skill might reasonably require in view of the significant false-positive rates associated with bioinformatic prediction programs, and the unpredictability jn the art associated with enzymatic processing in vivo.

The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function. Function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived therefrom by Dicer-catalyzed processing, which information is mined from raw genomic sequences.

Accordingly, the skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al. GenBank Accession No. AZ593982, published online at NCBI on December 13, 2000.

As shown by the alignment below, Dunn et al. taught a vector comprising a sequence encoding and complementary to SEQ ID NO:348. Accordingly, the prior art disclosed the instantly claimed vector.

```
>gb|AZ593982.1|  1M0405M14R Mouse 10Kb plasmid UUGC1M Library Mus musculus genomic
clone UUGC1M0405M14 R, genomic survey sequence.
Length=701

 Score =  152 bits (82),  Expect = 1e-34
 Identities = 88/91 (96%), Gaps = 0/91 (0%)
 Strand=Plus/Plus

Query  1    CCTGCTCCCGCCCCAGCAGCACACTGTGGTTTGTACGGCACTGTGGCCACGTCCAAACCA  60
            ||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  29   CCTGCCCCCGCCCCAGCAGCACACTGTGGTTTGTACGGCACTGTGGCCACGTCCAAACCA  88

Query  61   CACTGTGGTGTTAGAGCGAGGGTGGGGGAGG  91
            ||||||||||||||||||| |||||||
Sbjct  89   CACTGTGGTGTTAGAGCGAGGGTATGGGAGG  119
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Claims 31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Birren et al., GenBank Acc. No. AC015918 "Homo sapiens chromosome 17 clone CTD-3165O8 map 17", published online by NCBI on March 27, 2003. (The reference contains a lengthy sequence disclosure. Applicant is provided with the first 3 pages disclosing features relevant to the rejection and a portion of the sequence

As shown by the alignment below, Birren et al. disclosed a human BAC clone (i.e., vector) comprising a sequence encoding and complementary to instant SEQ ID NO:348 and 4233864. Accordingly, Birren et al. anticipates the instant claims.

```
>gb|AC015918.16| Homo sapiens chromosome 17 clone CTD-3165O8 map 17, 21 unordered
pieces
Length=220581

 Score =  169 bits (91),  Expect = 2e-39
 Identities = 91/91 (100%), Gaps = 0/91 (0%)
 Strand=Plus/Minus

Query  1       CCTGCTCCCGCCCCAGCAGCACACTGTGGTTTGTACGGCACTGTGGCCACGTCCAAACCA  60
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  40348   CCTGCTCCCGCCCCAGCAGCACACTGTGGTTTGTACGGCACTGTGGCCACGTCCAAACCA  40289

Query  61      CACTGTGGTGTTAGAGCGAGGGTGGGGGAGG  91
               ||||||||||||||||||||||||||||||
Sbjct  40288   CACTGTGGTGTTAGAGCGAGGGTGGGGGAGG  40258
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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birren et al., GenBank Acc. No. AC015918 "Homo sapiens chromosome 17 clone CTD-3165O8 map 17", published online by NCBI on March 27, 2003, as applied to claims 31 and 33 above in view of:

1. Venter et al. (US Patent 6,812,339)
2. Buck et al. (Biotechniques (1999) 27(3): 526-538);
3. Hogan (US Pat. 5,541,308, July 30, 1996); and
4. Brown (1998) "In situ hybridization with riboprobes: An overview for veterinary pathologists" *Vet. Pathol.* 35:159-167.

Claim interpretation:

The claims read on DNA and RNA probes and primers and vectors thereof.

The rejection:

Birren et al. is relied on for the reasons given above in the rejection under 35 USC 102. As shown by the alignment below, Zhao et al. taught an isolated 220,581-nucleotide DNA

sequence and BAC clone thereof comprising a sequence complementary and identical to instant SEQ ID NO: 348 and 4233864.

The use of nucleic acid probes and primers for research purposes was well established in the prior art.

For example, in analyzing genomic sequences, Venter et al. the use of probes and primers to detect and amplify genomic sequences. The probes and primers may be designed to hybridize to either strand. It is said a probe or primer typically comprises a substantially purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides, and that the primer and probe sequences can readily be determined using the sequences disclosed.

While Venter et al. does not teach probes and primers complementary to or comprising instant SEQ ID NO:6527 or 15 or their complements, in view of the disclosure of Buck et al., it would have been obvious to one of skill in the art at the time of invention that almost any complementary sequence of essentially any length suitable for detection of a nucleic acid could have been used to detect the sequences disclosed in GenBank Acc. No. AC015918.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs,

Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

Because primers and probes bind to their targets according to the same principles, it would be obvious to one of skill that each may be used according to the same purpose with the expectation each would bind the complementary target, whether via Northern blotting or in solution. In fact, one of skill would have even greater expectation of success given that probes need simply bind via Watson-Crick base-pairing and do not need to be extended as during PCR.

In view of the teachings of Buck, sequencing primers can be synthesized essentially anywhere along a given sequence of interest, and under optimal conditions they will reasonably be expected to perform adequately to yield sequence data. See page 533, left column, first full paragraph, and paragraph bridging pages 535 and 536. It would have been obvious to select a primer length of 22 nucleotides because those of ordinary skill normally use sequencing primers of 19-24 nucleotides in length (see Buck abstract). Accordingly, any 22 nucleotide fragment represented in either strand of the vector is considered to be obvious.

Further, the parameters and objectives for generating probes were well known in the art at the time the invention was made. For example, Hogan taught methods for generating target specific primers (col. 6-7, lines 50-67, lines 1-12), and provides extensive guidance for the selection of primers and probes. Hogan taught that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (column 10).

Brown taught methods for making and using single stranded RNAs of virtually any length less than about 500 nt for detection of nucleic acids *in situ*. Brown also cites several other references pertinent to the riboprobe art.

Therefore it would have been prima facie obvious at the time of invention to make and use DNA and RNA probes and primers of essentially any length against essentially any region of the sequence disclosed by Birren et al. for purposes of further characterizing said sequence and investigating the expression of said sequences as part of standard laboratory research with the anticipated success of detecting and or amplifying the corresponding sequences. It would further have been obvious to make and use vectors encoding said primers as an easily accessible, economical, and renewable source of said probes and primers.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Louis Wollenberger/
Examiner, Art Unit 1635
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